

# AMERICAN JOURNAL OF PHARMACY AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

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Vol. 112.

OCTOBER, 1940

No. 10

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Annual Subscription, \$3.00

Foreign Postage, 25 Cents Extra

Single Numbers, 30 Cents Back Numbers, 50 Cents

Entered as Second-Class Matter at the Post Office at Philadelphia, Pa.,  
Under the Act of March 3, 1879

Acceptance for Mailing at Special Rate of Postage Provided for in Section 1103  
Act of October 3, 1917. Authorized February 15, 1920

# E D I T O R I A L

On these pages the editor offers his opinions, unshackled by advertising patrons and unrestrained by anything save a sense of the decent and the truthful. The editor, alone, is responsible for their type, their tone and their tenor.

## TEACHING "THE THEORY OF PHARMACY"

THE subject of Pharmacy is unique in the scope of its teaching terrain. For into its purview must come something of nearly every subject taught in the curriculum. It is older as a whole subject than any other subject in the curriculum, for in a sense it mothered most of the other sciences.

Chemistry as an orderly subject, is indebted for much of its progress to Pharmacy, and particularly so in its early days. Botany likewise received its systematic start at the hands of searchers for plant medications. The background of Pharmacy is therefore old and complicated, and its history unique and instructive.

I say instructive advisedly, for although it was said by someone, that those who make history are too busy to write about it, a study of the history of Pharmacy is instructive, and its applications should be inspiring and constructive.

A brief outline of this history should be part of every course in Pharmacy. The terminology or nomenclature of the course is as diversified in its roots and origins as if it had come from the tower of Babel, hence the value and need for some knowledge of the Romantic and some of the less romantic modern languages.

The arithmetic of Pharmacy is of course a kindergarten study compared to the higher mathematics of physical chemistry, but it needs nevertheless to be well taught, and well learned, for it is an arithmetic that in practice deals a lot with life and death.

I often used to marvel, as I marked examination papers in the arithmetic of Pharmacy, how by the reckless deposit of graphite on cellulose, the population of Philadelphia suffered with every examination, a great decimation.

Chemistry, in all of its basic phases, to say nothing of its newer and more intricate aspects, seeps into every corner of the teaching of Pharmacy *per se*. Tests for identification of remedial substances; tests to limit impurities, assay processes, prescription incompatibilities; all of these and more, call for a fair knowledge of the subject.

And although we who teach Pharmacy should be glad to presuppose that the student knew all the Chemistry necessary to understand our work, we all know that in spite of good teaching in the Chemistry departments it becomes necessary for us, in the language of the professor, to "recapitulate" a great deal.

For instance, in discussing pH in connection with the diagnostic pharmaceutical "Phenolsulfonphthalein," we happened to mention the terminal exponents 0 and 14, and explained them as the normals for the acid H (1 gm. per 1000) and the alkaline OH (17 gm. per 1000). They had all been taught this fact before, and adequately, but *correct* repetition in the theoretical pharmacy course was, as clinically proven, definitely necessary and valuable.

The same thing is true of Physics. The physical constants, used as criteria of identity, quality and quantity, must be often rediscussed by the Pharmacy department as they involve themselves in so many specific problems in the field. Likewise apparatus and manipulation must have our attention. All of these things we must sometime re-teach and as accurately, though as simply as we know how. Indeed, because of the arrangement of the curriculum, we must often anticipate the other departments in considering some of these factors.

And we find that our students suffer if we accept it as a foregone conclusion that they already know these things. Actually an accurate repetition of them, though it occurs in two or three departments, hurts none and benefits many.

Physiology, Botany, Materia Medica, especially posology, are likewise involved in the theory of Pharmacy. "Stomachus" is the prosaic, "carcassy" official title of a new remedial in the present Pharmacopoeia. It is the defatted, desiccated stomach of the very unorthodox pig, and used in the treatment of pernicious anemia. Likewise are the mammalian liver and irradiated ergosterol now officialized. But these things have to be explained to the class, and they cannot be adequately explained unless there is involved some physiology, some physics and some chemistry perhaps, and we know from experience that the student, although he may know the particular phases of these subjects which apply here, must nevertheless have them spread all over the departmental minutes in order to have them register properly.

And this co- and inter-departmental teaching is far more valuable than that method of teaching which pigeon-holes isolated facts in a cranial roll top desk. Have we not been told by certain or by un-

certain students that they do not do well in Pharmacy examinations unless they are in the Pharmacy room. Nor can they in the Chemistry test, unless they gaze into the friendly face of the professor of Chemistry, whose *aura* energizes them to chemical thinking and none other. That, I submit, is not the fault of the professor.

What we should get over to our student body is that what is truly told in one department is equally accurate elsewhere, though it may differ a lot in the telling.

Accordingly, and in conclusion, it seems to me that we should admit this interdependence of the departments, and having done so, we should seek to correlate and coordinate their work, their always-accurate-work, in such a manner as to bring the greatest possible benefit to the student body and to the institution.

It is ridiculous to assume that any course or any department is more important, or less important than any other course or department in an institution. Every course, every branch, deserves our best attention.

IVOR GRIFFITH.

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### **PHARMACY SECTION**

#### **American Association for the Advancement of Science**

The next meeting of the American Association for the Advancement of Science will be held in Philadelphia during the week, December 27, 1940, to January 2, 1941. The program committee of the pharmacy section is planning for two sessions to be held in the morning and on the afternoon of Saturday, December 28, at the Bellevue-Stratford Hotel.

Scientific workers in pharmacy are invited to submit the title of papers which they wish to present before the section at an early date. Papers are usually limited to reports of the results of original investigations. The time allowed for the presentation of papers depends on the length of the program, usually fifteen to twenty minutes are allowed for each paper. Lantern and blackboard facilities will be provided if requested.

Send all communications to:

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University of Minnesota,

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## ORIGINAL ARTICLES

### EFFECT OF INTRODUCTION OF THE HALOGENS INTO THE PHENOL MOLECULE ON TOXICITY TO GOLDFISH.

#### III. MONOIODOPHENOLS

By W. A. Gersdorff and L. E. Smith

[Contribution from the Bureau of Entomology and Plant Quarantine,  
U. S. Department of Agriculture.]

#### Introduction

THE effect of the introduction of the chlorine atom (1) and of the bromine atom (2) into the phenol molecule on toxicity to goldfish with respect to the two variables concentration and survival time has been reported. This paper presents the results of similar studies on the effect of the iodine atom.

*o*-Iodophenol, which was purchased from the Eastman Kodak Company, was distilled under reduced pressure and the fraction distilling at 185 degrees at 160 mm. and having a melting point of 40 degrees was used. *m*-Iodophenol was prepared by the method previously described (3). *p*-Iodophenol was prepared by the procedure given by Dains and Eberly (4).

Toxicological tests were made with these substances, the general method having been described in a previous paper (5). Goldfishes of a single lot, weighing between 2 and 4 gm. each, were used as the test animals and the same temperature,  $27.0 \pm 0.2$  degrees, was maintained. All the substances formed clear test solutions at the concentrations used. They were prepared in the same manner as described in the study of the chlorophenols.

Because the goldfish were from the same lot that supplied the test animals for the studies on the chlorophenols and the bromophenols, the results reported herein may be compared with those obtained with those compounds as well as with the standard substances used for comparison, phenol and rotenone. The latter were reported with the study on the chlorophenols.

#### Experimental Results

The results are assembled in Table 1. A graphical comparison of the toxic action as expressed by these data is afforded by the survival-time and velocity-of-fatality curves in Figures 1 and 2. As

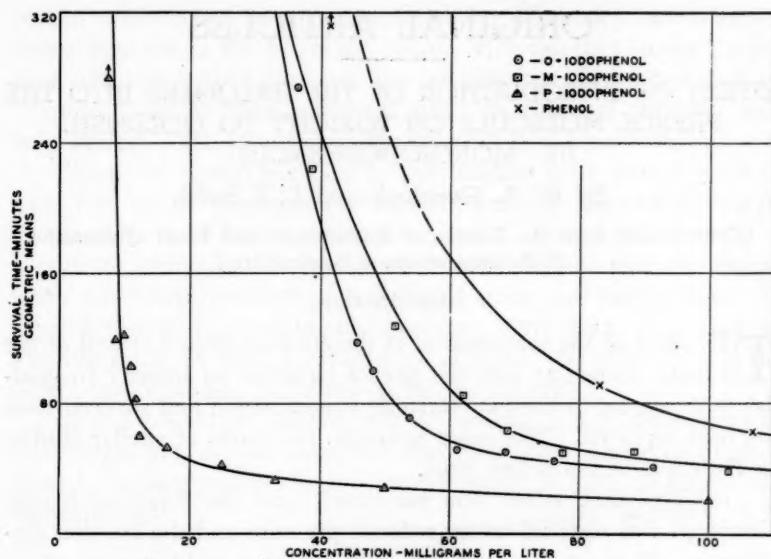


FIGURE 1 - SURVIVAL-TIME CURVES

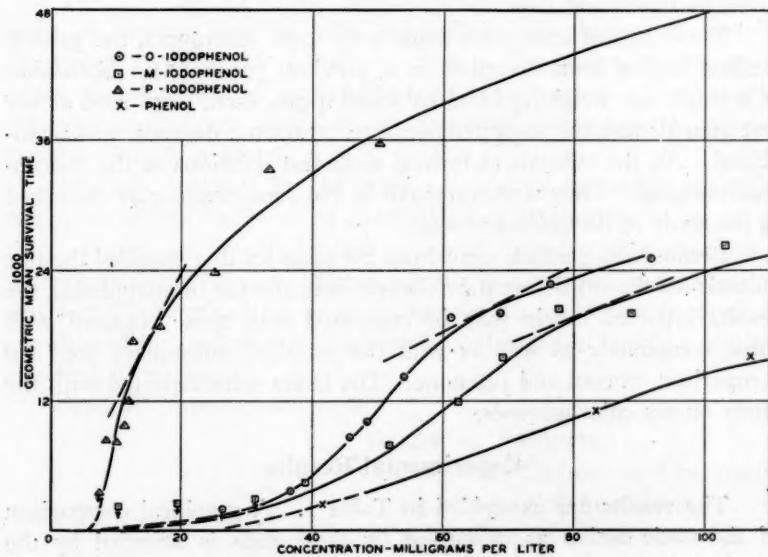


FIGURE 2 - VELOCITY-OF-FATALITY CURVES

in previous studies on phenolic compounds, the geometric rather than the arithmetic mean survival time was selected as the most suitable form of average and was used in the drawing of the graphs. Where desired in locating portions of the velocity-of-fatality curves, intermediate points were obtained by interpolation on the survival-time curves. The indefiniteness of the curves near the thresholds is indicated in Figure 2 by dotted lines.

TABLE I

TOXICITY OF THE IODOPHENOLS TO GOLDFISH AT  $27^{\circ} \pm 0.2^{\circ}$ 

Compound	Mean and concen- tration	Mean length	Mean weight	Fishes of fishes	Mortality	Mean survival time <sup>2</sup>	1.000 ÷ Geometric mean	
Milligrams per liter	Fishes used	Milli- meters	Grams <sup>1</sup> Per cent.	of fishes	8 hours	Arithmetic Minutes	Geometric Minutes	survival time
<b><i>o</i>-Iodophenol</b>								
91.6	8	49	3.5	100	41±3	40× or ±1.07	25.0	
78.3	10	46	3.0	100	45±2	44× or ±1.05	22.7	
68.7	10	47	3.1	100	50±1	50× or ±1.02	20.0	
61.1	11	47	3.1	100	51±1	51× or ±1.02	19.6	
53.9	12	45	2.8	100	72±3	71× or ±1.04	14.1	
48.2	11	47	3.1	100	102±5	100× or ±1.05	10.0	
45.8	12	47	3.1	100	145±22	117× or ±1.11	8.55	
36.6	12	44	2.6	83	309±28	274× or ±1.12	3.65	
26.2	12	8	8	>500	>500		<2.00	
9.2	13	8	8	0		Very slight toxic effect		
<b><i>m</i>-Iodophenol</b>								
155.	10	45	2.8	100	31±1	31× or ±1.03	32.3	
103.	11	44	2.6	100	38±1	38× or ±1.03	26.3	
88.7	10	44	2.6	100	51±1	50× or ±1.03	20.0	
77.6	9	45	2.8	100	50±2	49× or ±1.04	20.4	
69.0	11	44	2.6	100	63±1	63× or ±1.02	15.9	
62.1	13	44	2.6	100	87±4	85× or ±1.05	11.8	
51.7	10	45	2.8	100	138±14	127× or ±1.10	7.87	
38.8	12	45	2.8	75	285±48	224× or ±1.22	4.46	
31.1	13	8	8	62	>350	>340	<2.94	
19.4	14	8	8	36	>470	>400	<2.50	
10.3	12	8	8	33	>530	>430	<2.33	
7.8	12	8	8	0		Very slight toxic effect		

## p-Iodophenol

100.0	8	45	2.8	100	$20 \pm 1$	$20 \times$ or $\div 1.03$	50.0
50.0	10	44	2.6	100	$29 \pm 2$	$28 \times$ or $\div 1.06$	35.7
33.3	12	46	3.0	100	$34 \pm 1$	$33 \times$ or $\div 1.04$	33.3
25.0	8	44	2.6	100	$43 \pm 2$	$42 \times$ or $\div 1.05$	23.8
16.7	14	46	3.0	100	$53 \pm 2$	$53 \times$ or $\div 1.03$	18.9
12.5	12	45	2.8	100	$61 \pm 2$	$60 \times$ or $\div 1.04$	17.5
11.8	13	45	2.8	92	$92 \pm 7$	$83 \times$ or $\div 1.07$	12.0
11.1	12	45	2.8	83	$151 \pm 30$	$103 \times$ or $\div 1.18$	9.71
10.0	13	46	3.0	77	$186 \pm 38$	$122 \times$ or $\div 1.21$	8.20
8.57	14	45	2.8	93	$143 \pm 16$	$119 \times$ or $\div 1.08$	8.40
7.50	26	3	3	46	$> 360$	$> 280$	$< 3.57$
5.00	12	3	3	0		No evident toxic effect	

<sup>1</sup> Estimated from length, which measurement excludes the caudal fin.

<sup>2</sup> The limits of error indicated are probable errors of the means. In the case of the arithmetic means they are differences from the means; in the case of the geometric means they are ratios to the means.

<sup>3</sup> The fishes were not measured but were of the same approximate size.

From inspection of the velocity curves it is readily seen that the iodophenols are considerably more toxic than phenol. They show this increase in toxicity in the following respects: They become toxic at much lower concentrations; they attain a higher maximal acceleration (rate of increase of velocity of fatality with increase in concentration); they maintain their maximal acceleration to relatively high velocities; and, as a result, they kill more quickly at the high-concentration end of their toxic ranges, that is, in the corresponding regions of nearly constant velocity.

The nature of these effects is the same as was found when chlorine or bromine was introduced, but it is at once apparent that the relative effects are quite different, except perhaps the effect on the threshold-of-toxicity concentration. Although the data are meager, little difference, if any, between the thresholds of these nine halogenated phenols is indicated. Likewise, if there is any difference between the minimal times of kill in the regions of practically constant velocity, it is so slight as to be unmeasurable except possibly for p-iodophenol. The differences become apparent, however, between these two extremes in the course of toxic action. The ortho and meta isomers change places in the order of toxicity and all three iodophenols are more toxic than the corresponding chloro and bromo compounds.

Like the effect of chlorine and bromine, the increased effect of the introduction of iodine is not proportionate when relative toxicity

is considered from each parametric aspect, as shown at the extremes of toxic action. The increased toxicity of the iodophenols over that of phenol is due to a shift in both concentration and time factors. The increased toxicity over the corresponding chloro- and bromophenols is due essentially to a shift in concentration effect alone.

### Quantitative Comparison of Toxicity

A measure of relative toxicity found serviceable in previous studies for comparing toxic action in which the parameters are disproportionate is the minimal product of concentration and survival time (6). This measure ignores the two difficultly determined tolerance parameters and considers toxicity only in the range of most efficient action with respect to the two variables. Its value may be obtained by calculation from the survival-time curve or determined graphically from the velocity-of-fatality curve by drawing the maximal tangent to the curve from the origin, as indicated in Figure 2 with broken lines. In the latter case the slope of this line, expressed in the units of the coordinates, will give the reciprocal of the minimal product.

The data for comparison by this criterion are given in Table 2. The minimal product of concentration and survival time is designated by  $c_m t_m$  and, since toxicity varies inversely with this value, its reciprocal is also given. Its coordinates,  $c_m$  and  $t_m$ , are given so that the region approximating this condition may be located readily in the graphs.

TABLE 2  
RELATIVE TOXICITY OF ROTENONE, PHENOL, AND THE IODOPHENOLS AT 27° C.

Compound	$c_m$ Milligrams per liter	$t_m$ Minutes	$c_m t_m$ Gram-minutes per liter	Toxicity	
				$\frac{1}{c_m t_m}$	Relative toxicity according to $c_m t_m$
Rotenone	0.100	215	0.0215	46.5	1.00
Phenol	104	63	6.55	0.153	0.00329
o-Iodophenol	66.5	49	3.26	.307	.00660
m-Iodophenol	83.0	49	4.07	.246	.00529
p-Iodophenol	15.0	56	0.840	1.19	.0256

From these data it is seen that the ortho isomer is one and one-fourth times and the para isomer five times as toxic as the meta

isomer. Placed according to this criterion, the nine halogenated phenols studied fall into the following ascending order of toxicity, the ratios when compared with phenol being given. Phenol, 1.00; o-chlorophenol, 1.15; o-bromophenol, 1.25; m-chlorophenol and m-bromophenol, 1.53; m-iodophenol, 1.61; p-bromophenol and p-chlorophenol, 1.87; o-iodophenol, 2.01; and p-iodophenol, 7.78.

### Summary

A study was made of the toxicity of the three monoiodophenols with respect to concentration and survival time at 27 degrees, and the results were compared with each other and with those for phenol, rotenone, the monochlorophenols and the monobromophenols. Goldfish of the same lot, weighing between 2 and 4 gm. each, were used as the test animals.

The introduction of the iodine atom into the phenol molecule, like that of the chlorine and that of the bromine atom, results in compounds having a mode of toxic action markedly different from that of phenol. Toxicity is affected with respect to both concentration and survival time.

According to the minimal product of concentration and survival time, which measures toxicity in the range of most powerful action, the relative toxicity of the iodophenols as compared with that of phenol is as follows: meta, 1.61; ortho, 2.01; and para, 7.78.

Due essentially to a shift in the concentration factor alone, the most pronounced differences between the iodophenols and the chloro- and bromophenols are: (1) Each iodophenol is more toxic than the corresponding compound containing chlorine or bromine. (2) The ortho and meta compounds have changed places, however, in the order of toxicity so that the latter is the least toxic of the iodophenols. (3) The para compound has a pronouncedly greater toxicity than its least toxic isomer, it being five times as toxic in the case of the iodophenols as compared with one and one-half times for the bromo- and chlorophenols.

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## WHY THE REGULATION OF FOODS AND DRUGS WAS HANDLED BY THE DEPARTMENT OF AGRICULTURE

By T. Swann Harding \*

NOW that the Food and Drug Administration is in the Federal Security Agency it seems of interest to inquire why its work ever arose in the Department of Agriculture. Periodically in the world's history certain unscrupulous individuals have found it profitable to tamper with the food, spice and drug supply. The history of adulteration is a long one, running far back to classic times when ancient Romans bemoaned the sophistication of their wines. The history of efforts to protect the food, spice and drug supply is quite as long.

For every so often abuses would get so bad that there would be an outbreak of literature on the part of fevered fanatics designed to show that the "guinea pigs" were being poisoned right and left. This sometimes appeared disguised as palpable fiction. You will find examples in Tobias Smollett's *Expedition of Humphry Clinker*. At other times the books purported to be factual exposés—and were often quite as fictional.

However, where all this smoke was there was some fire. The worst charges made were never true, but things were usually bad enough to cause a clean up and some good resolutions. Sometimes regulatory laws were passed. Sometimes, as in the fourteenth century, dealers tried self-regulation. In this case they appointed agents called "garblers" (literally sifters) who would pass upon the condition of bales of merchandise and examine lots of drugs and spices under oath, removing adulterants at specified rates. The garblers attested the accuracy of the weight of the product and of the adulterants removed.

In due time, though, human nature being what it is, the garblers themselves would become corrupt. We find published in 1592 a tract entitled: *A Profitable and Necessarie Discourse, for the Meeting of Bad Garbelling of Spices, Used in these Days*. The tract dealt mainly with the shameful pepper situation. But from such efforts sprang our modern attempts to regulate the labels and advertisements of foods, drugs and cosmetics.

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\*Falls Church, Va.

Label regulation in the United States is today in the hands of the Food and Drug Administration which was a bureau in the Department of Agriculture until July 1, 1940, when it was transferred to the Federal Security Agency. People often wonder how this governmental function ever happened to land in the Department of Agriculture, forgetting, perhaps, that this department is charged with the general protection of the food supply of the nation. But the true story of how this form of regulation began in that Department is an interesting one and it deserves telling.

To find the story one must start with the printed annual reports of the commissioners of patents. For in one of the very earliest of these, that for 1837, there is considerable mention of agricultural matters. January 22, 1839, Commissioner of Patents Henry L. Ellsworth, wrote to Isaac Fletcher of the House of Representatives stating that we should have some agency in the Federal Government to serve agriculturalists. He spoke in this letter of rapid advances in agricultural technology and of how the food supply could be increased by proper seed selection. This was in answer to a letter of inquiry from Congress.

As a sort of reply to this letter Ellsworth received permission from Congress (as a rider to the census bill being considered) to expend \$1000 out of the Patent Office's incoming funds from fees upon the collection and distribution of good seeds and agricultural statistics. That was the Department of Agriculture in embryo in the Patent Office in the Department of State.

In his report for 1841, issued in January, 1842, Ellsworth already spoke of the necessity of using agricultural chemistry to promote increases in food production. He told of testing a new method of producing sugar from cornstalks by picking off the ears before they matured and maturing the stalks instead—a method long since forgotten. In 1843, Ellsworth was entranced by electricity, and wrote of the medicinal applications of electric batteries and how the "electromagnetic fluid," which gilds metals and separates beautiful ores, also dissolves bladder stones painlessly, rescuing victims from death in agony or a painful operation! At that time, Ellsworth said, an experiment had been made in Paris also of illuminating the streets "by means of the electric spark."

Ellsworth's report ran 330 pages, and was largely concerned with discourse on agricultural matters, crops and foods. He spent \$444.67

to run the agricultural section of the Patent Office. As early as 1844 Commissioner Ellsworth had his chemist analyze certain corn meals and concluded that some of these were difficult for dyspeptics to digest, due to their high oil content.

In 1848, Commissioner of Patents Edmund Burke reported a special Congressional appropriation of \$1000 which was used to finance a chemical study by Prof. Beck of New Brunswick on the effects of storage and sea voyages upon flour and meal. In 1849, the Patent Office went into the newly created Department of the Interior. Thomas Ewbank, commissioner, reported to Millard Fillmore and mentioned the necessity for studying the preservation of foods by different methods.

In 1861, Commissioner of Patents D. P. Hollaway made a prolonged plea in his report for the setting up of a Federal Government Department to serve agriculture. The very next year, May 15, 1862, President Lincoln signed the bill that brought the Department into existence. Its first commissioner was Isaac Newton, who had previously been head of the agricultural section in the Patent Office. Its first professional employe, appointed August 21, 1862, was Charles Wetherill, a chemist. Commissioner Newton had the greatest faith in agricultural chemistry.

One of the primary reasons that the Department came into existence when it did was the necessity for producing food economically and efficiently during the Civil War. Hence the Department concerned itself with food problems at its very beginning. It continued to do so.

In 1868, Commissioner of Agriculture Capron reported that his chemist had analyzed mineral waters and pharmaceutical preparations. In 1873, Frederick Watts reported to President Grant as agricultural commissioner. His report was very concise but he mentioned that his chemist, Wm. McMurtrie, was analyzing not only fertilizers and soils but also wines and cereals.

In 1878, Wm. G. Le Duc was commissioner and Peter Collier was chemist. The chemical laboratory was then confined to two small rooms and a closet and could not do as much as it should. The chemist himself got \$2000 a year but actually received only \$1900 of that, due to deficient appropriations; his assistant got only \$1400 of his rightful \$1600 that year. The laboratory had analyzed cream puffs for poison, adulterated tea, and suspected bologna sausage. This work it had done for the health officer of the District of Columbia.

Collier and his assistants had also looked into coffee and tea. They had examined certain coffee substitutes, some baking powders, some butter and oleomargarine and many other foods. Finally they had examined a tonic which they named: "Boneset"; they gave its formula but refrained from disparaging remarks. In 1880, Le Duc was still commissioner and Peter Collier's report was a thing of grandeur, 143 closely printed pages with 13 large figures showing graphs in colored inks, all folded in.

The chemical laboratory was "now confined to a room in the present building 20 feet square, with two basement rooms of the same size, and a small closet." Hence work accumulated that could not be done, but Le Duc felt this "national laboratory of a great people" should have more space, better facilities, and a larger staff. There was now a chief chemist with 11 assistants, mostly young chemical graduates.

On page 616 of this report for 1880 we find the following significant statement:

#### "ADULTERATIONS OF FOOD

We have had frequent communications respecting the adulteration of foods, in respect of which our correspondents err in presuming that the remedy therefor lies with this Department. Inquiries are made whether, if there be no more ready remedy, it is not within the power of Congress to pass a stringent law making it a crime to manufacture certain spurious articles or to adulterate genuine ones. Admitting the subject to be one of great and universal interest, we have only been able to say to our correspondents, that under the present standard of commercial morality, nothing is safe from adulteration; that the action of the general government is limited to imported articles, and chiefly to drugs; that the power of the government ceases with the custom-house; and that the general regulation of the subject is left to the several States, in most of which there are laws designed to remedy the evil, which, however, can only be done effectually by a rigid system of inspection. Merely prohibitory laws are of little value against human ingenuity and cupidity."

Already the chemist was making analyses of so-called concentrated stock feeds and veterinary remedies and even of a magic metal polish. He published the results giving the names of the products and their manufacturers, as well as their analyses, and slyly hinting that most of them were neither worth the price asked nor capable of living

up to their advertising claims. In short, farmers began to be protected from fake cattle foods and veterinary remedies—in their capacity as consumers.

In 1883, when George B. Loring was Commissioner of Agriculture, we read that a young chemist named Harvey W. Wiley had made an investigation of sorghum cane which was reported therewith. Moreover, a study of butter and its adulterations had begun in the chemical laboratory and plans existed for its further prosecution. The idea was "to aid the dairy interest in establishing a standard for good butter and *to protect consumers against fraud.*" Please note the significant words italicized by the present writer.

In 1884, Wiley reported to Loring results both on sugar plants and on adulterated butters, now in his capacity as chemist, to which position he had meanwhile been appointed. In 1885, Commissioner Norman J. Colman reported that the chemists now had food adulteration in general under study—beginning with butter and honey. He wrote: "It is highly desirable that some general standard of purity for foods should be established and that uniform methods of examination for adulterations be agreed upon." The work already showed some of the character and extent of such adulterations, a legal standard was advocated for the fat content of butter, and Wiley had an article in the report on honey and its adulterations.

Obviously the great American public, this time by correspondence, had made its needs known and the Department had responded by extending its services into the field indicated—food adulteration. In 1886, one of Wiley's assistants, one Clifford Richardson, reported on the adulteration of spices and condiments, thus getting back to the task the old garblers had muddled in another age. In 1887, Wiley was examining wine, beer, coffee, tea, chocolate and baking powders.

Norman J. Colman was our last Commissioner of Agriculture. In his final report (1888) he said he was alarmed by food adulterations disclosed by his chemists, the results of the investigations now having been published in *Bulletin 13*. He said the fraud was mainly financial in character (rather than detrimental to health); hence the work was of fundamental importance to farmers. For passing off the less for the more valuable foods injured the reputation, standards of production and business of agriculturalists.

In 1889, the Department of Agriculture achieved cabinet rank and the first Secretary was J. M. Rusk, except for 26 days that Colman

served automatically. Right off he wrote that he found "the chemical laboratory crowded into a damp, illly ventilated and wholly unsuitable basement, originally intended no doubt for storage purposes, and its work in certain investigations restricted because of the offensive fumes from such analyses, and because of the dangers to human life and limb from explosions of gases and other causes." His chemist continued to report on food adulterations. That chemist of course continued for many long years to be Harvey W. Wiley.

In 1891, Rusk remarked in his report that "a system of inspection for all articles of food is extremely desirable." Wiley reported on sorghum, the muck lands of Florida, butter adulterants, meat preservatives, tea and cocoa adulterations. In 1892, Rusk suggested that certain units in his department, including that of chemistry, become bureaus, but that did not yet occur. Wiley emphasized food adulterations in his report but also did not forget to discuss beets.

He continued this work for the years following. James Wilson became Secretary of Agriculture in 1897. In 1900 he reported that his chemists now cooperated with the Pure Food Congress of the United States and helped to model pure-food laws to control the traffic in adulterated foods. In 1901, Wiley's unit became the Bureau of Chemistry.

In 1903, we find Wiley hot after food preservatives and also preparing to enforce the new import food act passed by Congress March 3, 1903. Wiley was also getting his famous "poison squad" ready and seeking volunteers. He wanted to study the effects of preservatives and coloring matters then used in foods upon the public health. In 1904, he and his staff were busy inspecting imports, running the poison squad and the enlarged food laboratory.

In 1905, Secretary Wilson reported unsurpassed agricultural prosperity. His chemists continued to study food standards, preservatives and food poisons. Wiley also reported on patent medicines. He said that there was abuse in the field of drugs offered for self-medication and that proprietary medicinal agents containing habit-forming drugs should be regulated. His work in cooperation with the Post Office Department, which closed the mails to frauds, had appeared to bring these matters to his attention. But he also mentioned some concoctions in detail, including a cosmetic—a complexion lotion.

In 1906, of course, Wiley's Food and Drug Law was passed. It gave him limited regulation of the labels of packaged food and drug

products but left advertisements unscathed. The personnel of his Bureau doubled between January 1 and June 30, 1907. Food and drug inspectors were appointed and a Board of Food and Drug Inspection came into existence. In 1908, the appointment of Walter G. Campbell (now Chief of the Food and Drug Administration) as Chief Inspector was announced in the report.

In 1909, James Wilson reported ever higher production by farmers and said this "must add much to the prosperity" of the agriculturalists. He noted the food and drug work but added that "'Adulteration' is an ugly word in the public mind," and intimated that he might like to hit upon some softer euphemism! He said 'we musn't make the new law an instrument of repression so let's have a Referee Board of Consulting Scientific Experts—which was duly appointed and later aroused Wiley's ire. Benzoate of soda and sulphur dioxide had an airing in the reports.

It is needless at this late date to go into the merits of a controversy that arose about this time. When he considered himself vindicated, Dr. Wiley spectacularly resigned and joined *Good Housekeeping*. In any case Wiley was a grand old war horse and we would not have had a law to regulate drugs and foods as soon as we did had it not been for this dominating personality. In 1912, his Bureau had grown from 20 employees in 1897 to 500 and it occupied its own six-story building.

As the years went by it proved increasingly difficult efficiently to pursue pure and applied research and regulatory work in the enforcement of the Food and Drug Law in the same unit. As the administrative problem became increasingly complex something had to be done. So in 1927, when W. M. Jardine was Secretary of Agriculture, the food and drug work was separated from the Bureau of Chemistry and placed in an agency by itself, first the Food, Drug and Insecticide and later the Food and Drug Administration, with Campbell as chief.

Since that time the Bureau of Chemistry (later combined with the Bureau of Soils, a union subsequently in part dissolved) has embarked on a huge research program of its own. It is now the Bureau of Agricultural Chemistry and Engineering.

Meanwhile the Food and Drug Administration has pursued its work with ever increasing efficiency. To cap the climax it managed, after a six-year fight on the part of militant consumers, to get a new

and stronger law to enforce—the Food, Drug and Cosmetic Act sponsored by the late Senator Copeland. Actually such a law had been advocated by chiefs of the Bureau of Chemistry from 1912-1917 on. The new law went into full effect in 1940. It extends protection to cosmetics and medical appliances while advertising comes under the Wheeler-Lea Amendment to the fair trade laws, enforced by the Federal Trade Commission. That roughly completes the story to date.

While it is true that the work of the Food and Drug Administration does deal with health, in certain important aspects, it also deals with the perpetration of financial fraud. In this way its functions naturally formed part of one of the basic functions of the Department of Agriculture—the protection of the American food supply.

In addition this work conserves the incomes of American farmers insofar as it runs fraudulent concentrated feeds and veterinary remedies out of existence. It protects the farmer in his capacity as consumer and enables him to spend his money more efficiently, thus indirectly increasing his income.

Lastly, insofar as the operations of the law tend to improve the quality of American foods they are in close harmony with another aim of the Department's service program. That program has increasingly concerned itself in recent years with the production of higher quality commodities and the checking of adulteration thus contributes to that end. That it also contributes to better nutrition of the American people is obvious.

Hence, it seems only natural that the work of the Food and Drug Administration originally began in the Department of Agriculture. Its departure into the Federal Security Agency by a Presidential reorganization order effective July 1, 1940, takes from the Department of Agriculture lines of work having a long history within its structure.

## THE SEPARATION AND DETECTION OF COCAINE IN COCAINE STOVAINE MIXTURES

By Charles Milos

[Contribution from New York Branch Laboratory of the Alcohol Tax  
Unit, Bureau of Internal Revenue]

**W**HEN Stovaine— $\text{CH}_3\text{CH}_2\text{C}(\text{C}_6\text{H}_5\text{COO})(\text{CH}_3)\text{CH}_2\text{N}(\text{CH}_3)_2\text{HCl}$ , the hydrochloride of benzoylethyldimethylamino-propanol is used as an adulterant for Cocaine ( $\text{C}_{17}\text{H}_{21}\text{NO}_4$ ) a separation of the components is often necessary for a positive identification of the Cocaine.

Cocaine and its salts give a feathery crystalline precipitate with platinic chloride in acid solution, which is characteristic for Cocaine, and may be observed and identified under the microscope. Gold Chloride ( $\text{AuCl}_3\text{HCl}$ ) also gives characteristic crystals with Cocaine and its salts.

Though gold chloride is a more sensitive test than platinic chloride for Cocaine, traces of impurities destroy its value, whereas, under similar conditions crystals are obtained with platinic chloride. (Stephenson Microchemical Tests for Alkaloids, Lippincott 1921; Allen's Commercial Organic Analysis, Vol. 7, 5th edition, Assoc. of Official Agricultural Chemists, 4th edition, 1935).

Stovaine with platinic chloride gives an amorphous precipitate. In mixtures where Stovaine predominates, the characteristic crystals given by Cocaine are completely obscured or modified beyond recognition.

A method of separation was worked out, whereby a mixture of Cocaine and Stovaine free bases dissolved in petroleum ether are extracted with a buffer pH 1.8. The buffer is prepared by mixing 10 cc. of 0.2N hydrochloric acid with 75 cc. of 0.2N potassium chloride. The greater part of the Cocaine and part of the Stovaine dissolve in the buffer. During the extraction the pH of the buffer increases. On the addition of more 0.2N HCl to this buffer and extracting with chloroform the greater part of the Stovaine is removed.

### Preparation of Standard Solutions

0.2 Normal Potassium chloride. Dissolve 7.456 grams of C. P. potassium chloride in 200 cc. of distilled water and make up to a volume of 500 cc. with distilled water.

0.2 Normal Hydrochloric acid. Take 100 cc. of a normal hydrochloric acid solution and dilute to a volume of 500 cc. with distilled water. Ten cubic centimeters of this solution should require 20 cc. of 0.1N sodium hydroxide for neutralization, using Phenolphthalein as an indicator.

### Method

Dissolve 0.1 gram of sample in 15 cc. of dilute acid. Transfer to a separator, make alkaline with ammonium hydroxide and extract twice with 50 cc. portions of petroleum ether. Collect the petroleum ether in a separator, wash with 5 cc. of water and discard the water.

Shake the petroleum ether twice with 10 cc. portions of buffer (10 cc. of 0.2N hydrochloric acid + 75 cc. of 0.2N potassium chloride) and combine the buffer solution in another separator. Discard the petroleum ether.

To the combined buffer solution add 3 cc. of 0.2N hydrochloric acid. Extract twice with 25 cc. portions of chloroform and discard the chloroform. The chloroform on settling should be clear or nearly so. If it is cloudy, reshake and allow to stand for some time.

Add ammonium hydroxide to the buffer solution until alkaline to litmus and extract with 50 cc. of petroleum ether. Wash the petroleum ether with 2 cc. of water, discard the water and filter the petroleum ether into a dish, and evaporate to dryness on a steam bath, using a fan.

To the residue in the dish add 2 cc. of normal butyl alcohol and again evaporate to dryness.

Dissolve the residue in a drop or two of dilute hydrochloric or acetic acid. Transfer to a slide and add a drop of platinic chloride solution. If cocaine is present its characteristic crystals can be observed under the microscope.

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### Summary

1. A method for the separation of cocaine from stovaine is given.
2. One milligram of cocaine in 100 milligrams of stovaine can be isolated and identified.
3. The molecular structure of cocaine is not altered.
4. Exact quantitative results are not obtained by this method.

## ABSTRACTS FROM AND REVIEWS OF THE LITERATURE OF THE SCIENCES SUPPORTING PUBLIC HEALTH

**The Spectrophotometric Determination of Vitamins D<sub>2</sub> and D<sub>3</sub>.** C. H. Nield, W. C. Russell and A. Zimmerli. *J. Biol. Chem.* 136, 73 (1940). Many color reactions have been reported for vitamin D but few have been determined for the quantitative determination of this factor. Of those reported the Brockmann-Chen (*Z. Physiol. Chem.* 241, 129 (1936)) method appeared the most promising. In this determination a yellow color is formed by the reaction of the vitamin with antimony trichloride in chloroform solution. Various workers have found that the chloroform solution of antimony trichloride is unstable, its sensitivity changing with time and that it must be free from alcohol and moisture.

The authors in studying the variation in sensitivity found that saturating the antimony trichloride solution with dry hydrogen chloride increased the sensitivity but the resulting reagent was extremely hygroscopic and difficult to handle. Addition of acetic anhydride eliminated this difficulty but it was effective only over narrow limits of concentration. The substitution of acetyl chloride for the hydrogen chloride and acetic anhydride eliminated the above disadvantages and produced a reagent that had all the favorable features of the reagent proposed by Brockmann and Chen, exhibited none of its inconsistencies and was three times as sensitive.

The reagent produces a yellowish pink color with vitamins D<sub>2</sub> and D<sub>3</sub> which reaches its maximum intensity within thirty seconds and is stable for from four to five minutes.

Using a Bausch and Lomb spectrophotometer the two vitamins exhibit identical absorption curves with a maximum at 500 m $\mu$ . At this wave length the  $E_{1\text{ cm.}}^{1\%}$  values for vitamins D<sub>2</sub> and D<sub>3</sub> are approximately 1800. The lower limit of vitamin that can be accurately determined is approximately 0.2  $\gamma$ . L. F. T.

**Dehydrated Castor Oil and Its Economic Importance.** D. H. Killeffer. *J. Ind. & Eng. Chem.* 32, 1466 (1940). During the past twenty years some forty-four million pounds of castor oil have been used on the average yearly. The uses of castor oil are of a varied

nature; medicinal, the manufacture of sulfonated oil, artificial leather, lacquers, and for lubrication purposes.

Many of these applications depend to an extent on the fact that castor oil does not dry or polymerize. In lubricants in order to form permanent mixtures with petroleum lubricants it is necessary to treat castor oil to increase its solubility. Formerly this treatment consisted of blowing air through the heated oil, resulting in dehydration through the loss of the hydroxyl group and a hydrogen from the neighboring methylene group. The air blowing, however, produced some oxidation in such manner as to destroy the effect of the additional double bond formed by such dehydration. A modification of this process is the use of a non-oxidizing mineral acid containing oxygen as a catalyst. In this operation no blowing is carried out and the oil is not oxidized resulting in a finished product containing two double bonds in each acid radical.

This type of dehydrated castor oil now behaves in an entirely different manner. Instead of being a permanent, non-polymerizing oil, its properties approach those of tung oil in drying, film forming and polymerizing ability. The acid of tung oil is characterized by three conjugated double bonds. In the castor oil molecule two conjugated double bonds may be produced by the dehydration process. About 25 per cent. of the double bonds in dehydrated castor oil are apparently in the conjugated position. There may be some difference in this proportion as produced by different catalyst and treatments and efforts are being made to increase it.

At least four manufacturers are producing and selling dehydrated castor oil for paint uses under the names "Isoline," "Dehydrol," "Synthenol," and "Castolene."

The possible demand for dehydrated castor oil serves to arouse interest in its domestic production. Much of the material from foreign sources has been absorbed by the war. The only areas in the United States where the castor plant may be advantageously grown are Florida and southern Texas, where the crop may be harvested three times yearly. Certain features with regard to the harvesting of the crop and its various by-products are presented. L. F. T.

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**Preservation of Sodium Thiosulfate Solutions.** F. J. Kirkish. *Chemist Analyst* 29, 68 (1940), through *Squibb Abstr. Bull.* 13, 1259 (1940). Chloroform has been found to be effective in stabilizing sodium thiosulfate solutions. In order to determine its effective-

ness two 500 cc. portions of 0.1 n. sodium thiosulfate were stored in dark brown glass-stoppered bottles under identical conditions except that 0.5 cc. of chloroform was added to one of them. The one containing chloroform lost only 0.1 per cent. of its original strength during the first three and one-half months as compared with 0.8 per cent. loss for the untreated material. Beyond this period, however, the chloroform loses its effectiveness.

L. F. T.

**Sterilization of Aqueous Solutions.** W. B. Weeden. *Hosp. Management* 50, 37 (1940), through *Squibb Abstr. Bull.* 13, 1263 (1940). In the sterilization of aqueous solutions it is necessary that each solution placed in the autoclave be put in containers of uniform size. As the result of careful potentiometric tests and temperature curves the following data were prepared to show the correct exposure periods for various sizes of thin Florence flasks: 2000 cc. flask, exposure period 20 min.; 1500 cc. flask, exposure period 15 min.; 1000 cc. flask, 15 min.; 500 cc. flask, 12 min.; 250 cc. flask, 8 min.; 125 cc. flask, 8 min.; 50 cc. flask, 6 min.; two-ounce ordinary thick glass bottles ordinarily used for procaine, 8 min. A period of exposure begins when the thermometer indicates 240 degrees F. and continues for the specified length of time during which the thermometer will slowly advance to a maximum of 250-4 degrees F. At the close of the period of exposure the heat should be turned off, the valve admitting steam to the chamber turned off and the exhaust valve from the chamber adjusted slightly open to a degree that will permit exhaust of pressure to zero in not less than seven to ten minutes. Using this method the fluid can exhaust its heat, without too violent ebullition, at the same rate at which pressure is reduced.

L. F. T.

**The Desivac Process for Drying From the Frozen State**  
E. W. Flosdorf, F. J. Stokes and S. Mudd. *J. A. M. A.* 115, 1095 (1940). During the past few years evidence has been accumulated which supports the value of human blood plasma or serum as substitutes for whole blood transfusion. The reduction in hemoglobin which patients can endure without danger is extreme and it is reduction in circulating blood volume which must be corrected promptly. The plasma proteins may be maintained in highly stabilized form by drying from the frozen state and as such they are instantly available

for use by dissolving in water to the original or to a more concentrated volume.

Some of the methods now employed for this type of drying are the lyophile (*J. Immunol.* 29, 389 (1935)), and the cryochem (*J. Immunol.* 34, 469 (1938)) procedures. In the lyophile process the water vapor is removed in vacuum by condensers maintained at the temperature of solid carbon dioxide, -78 degrees C. A pressure well under 0.2 mm. is maintained. In the cryochem process a regenerable chemical desiccant, specially prepared calcium sulfate is used for removal of water vapor. The pressure in this technic can be as high as from 1 to 2 mm.

The authors describe a new apparatus which is entirely mechanical in operation for such drying procedures.

Pumps of large volumetric capacity are used which instead of operating with a static oil seal circulate the oil used in the vacuum seal. This oil has its water removed by continuously passing it through a centrifuge. In this manner a low vapor pressure is continuously available for the high vacuum seal of the pump and water vapor is withdrawn from the high vacuum space as rapidly as it is evaporated directly to the atmosphere and is discharged there in the liquid phase.

The system is so efficient that it will operate at 4.5 mm. of mercury pressure and still keep the materials frozen solid by loss of latent heat of evaporation. By the end of the drying cycle the pump finally produces a pressure below 200 microns which readily removes the last traces of water from the material so that residual moisture is less than 1 per cent.

L. F. T.

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**Pitressin Tannate in Oil in the Treatment of Diabetes Insipidus.** J. A. Greene and L. E. January. *J. A. M. A.* 115, 1183 (1940). It has been known for several years that solution of posterior pituitary controls the manifestations of diabetes insipidus. The solution may be administered hypodermically or sprayed into the nose. Furthermore, the intranasal insufflation of the powdered whole gland controls the symptoms.

The subcutaneous administration of the solution of posterior pituitary or pitressin appears to be the most effective method of treatment. The disagreeable side effects such as pallor, diarrhea, palpitation, etc., and the frequency of injection required often make the prolonged use of such therapy undesirable. The nasal insufflation

of the whole gland is often more convenient and less painful but in the severe case it may be required from six to eight times a day and at least one time during the night.

Methods to produce slow absorption of hormones have been shown to be desirable in certain endocrine deficiencies. With this in mind the authors have tried clinically a suspension of pitressin tannate in oil administered subcutaneously.

The duration of the effect in patients was found to be from thirty to eighty-two hours and there were no disagreeable after effects.

**Grapefruit Seed Oil.** A. J. Nolte and H. W. von Loesecke. *J. Ind. & Eng. Chem.* 32, 1244 (1940). Commercial production of grapefruit seed oil is a new industry in Florida. The seeds are readily collected from canneries where they are separated during the process of canning grapefruit juice and sections. The potential yield of seeds from such canneries during the 1938-1939 season amounted to 15,601 tons from which almost four million pounds of crude oil could be separated.

In the production of grapefruit seed oil the fresh seeds are dumped into a tank with water and allowed to undergo fermentation which loosens the slimy coating and adhering pulp. This usually requires from twenty-four to forty-eight hours and is accelerated somewhat by the addition of small amounts of phosphate such as tricalcium phosphate. If the seeds remain too long in the tank they become putrid and yield a foul-smelling oil. After soaking, they are drained on a screen and steamed, then dried in rotary driers until the moisture content has been reduced to 2.5 to 3.0 per cent. The oil is then expressed and is filtered through a plate and frame press. The press cake is sold either as fertilizer or stock feed ingredient.

The unrefined oil has a reddish brown color, a nut-like aroma, and an intensely bitter taste. It becomes cloudy at 15 degrees C., pasty at 4 degrees C. and solid at -10 degrees C.

The experimental refining, bleaching and "wintering" gave a bland, light, tasteless oil having a sp. gr. of 0.919,  $N_D$  1.4700, acid value 0.26, saponification value 192.2, iodine number (Hanus) 109.2.

The bitter principle which was removed in the refining process by the caustic alkali was extracted from the soap stock following its acidification and is believed to be identical with lemonin described by Bernay in 1841 as a constituent in the seeds of several varieties of citrus fruits.

## BOOK REVIEWS

Done by persons, unafraid to upbraid, but perfectly willing to give praise where praise is really due.

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**Chemical Formulary (Vol. IV).** H. Bennett. 638 pages. Chemical Publishing Co. \$6.00.

This fourth volume of the 1939 Chemical Formulary presents a considerable number of technical formulas in practically every field; pharmaceuticals, cosmetics, insecticides, detergents, polishes, beverages, inks, etc. It represents not a revision of the three preceding volumes, but rather an addition to formulas presented therein.

It will be undoubtedly a helpful reference to those engaged in product formulation serving to give several formulas that may be used either for finished products or as starting points for experimentation.

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**Utilization of Fats.** H. K. Dean. Chemical Publishing Co. \$6.00.

The contents are subdivided as follows: Constituents and Properties of Fats; Analytical Methods; Classification; Composition and Analysis of Fats; Artificial Fats; Extraction and Refining of Fats; Edible Fats; Paint and Varnish Oils; Soaps and Fatty Acids; Miscellaneous Applications.

The author has considered certain new phases of the chemistry and constitution of the glycerides as well as the changes produced during oxidation and polymerization. In addition to such theoretical considerations, there is also some appropriate practical information of value to the technologist. The experience of the author gained in both fundamental as well as applied research on this subject has been of definite assistance in the compilation of this book.